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(54) Title: **LEUKOTRIENE ANTAGONISTS FOR ORAL SQUAMOUS CELL CARCINOMA**

(57) Abstract

This invention provides methods for the treatment or inhibition of oral squamous cell carcinoma which comprises administering to a mammal in need thereof an effective amount of a compound having activity as a leukotriene B₄ antagonist.

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Title

LEUKOTRIENE ANTAGONISTS FOR ORAL SQUAMOUS CELL CARCINOMA

5

Background of the Invention

10 Squamous cell carcinoma is the most common malignant neoplasm of the head and neck. It constitutes at least 75% of head and neck cancer in which patients show a high incidence of immunologic deficiencies and inflammatory symptoms. Despite improvements in the treatment modalities over the past 40 years, the 5-year survival rate of approximately 30% has not changed in the same period.

15 Oral squamous cell carcinoma has been linked to excessive cigarette smoking and alcohol abuse, both individually and in combination. Other factors associated with oral cancer include poor dental hygiene and malfitting dentures or broken teeth that cause chronic mucosal irritation. Occupational hazards include chronic dust exposure among woodworkers, which has been associated with cancer of the nasopharynx, and exposure to nickel compounds, which increases the risk of paranasal sinus cancers.

20 25 Epstein-Barr virus (EBV), the etiologic agent of infectious mononucleosis, has been associated with nasopharyngeal carcinoma. Other viruses have also been implicated, including oral herpes simplex virus type 1 and endogenous oncornaviruses.

30 Radiation exposure, as well as dietary deficiencies, may also predispose persons to head and neck cancers.

35 About 90% of oral cancers are detected in only a few high-risk sites; the floor of the mouth, the ventrolateral aspect of the tongue, and the soft palate complex. Buccal and labial vestibular carcinoma should be considered in people who use smokeless tobacco.

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Cancer of the head and neck occurs in four major anatomic sites: the oral cavity, pharynx, larynx, and nasal and paranasal sinuses. These sites are subdivided into various component regions. The most common sites of disease 5 are the oral cavity and the oropharynx, which account for slightly less than 50% of cases, followed by the larynx, which accounts for about 30% of cases.

Early, asymptomatic oral cancer appears most often as a red (erythroplastic) lesion. Squamous cell carcinoma, not 10 diagnosed in its earliest stages appears later as a deep ulcer with smooth, indurated, rolled margins, fixed to deeper tissues. Biopsy is necessary to diagnose carcinoma.

Squamous cell carcinomas are often diagnosed early because such cancers lead to local symptoms such as pain, 15 hoarseness, and difficulty in swallowing. In many cases, however, diagnosis is delayed because local symptoms or pain from nerve involvement does not occur until a large primary tumor develops. In such cases, regional nodal metastases may be the initial manifestation. Distant metastases rarely 20 occur without locally advanced primary disease or nodal involvement.

Head and neck cancer may be a panmucosal disease of the upper aerodigestive tract; additional silent synchronous primary lesions occur frequently. Patients with such a 25 clinical picture are predisposed to additional primary head and neck cancers at a later date (the incidence is approximately three to five percent a year).

Although there are few tumor markers for head and neck cancer, the serum ferritin level is reported to accurately 30 reflect the stage and course of disease. (Ferritin is a major iron-storage protein of human tissues and is found in small quantities in the serum.) However, an elevated serum ferritin level is not specific for head and neck cancer; its level is also elevated in other cancers and in nonmalignant 35 conditions.

Levels of antibodies to EBV in both established and occult nasopharyngeal carcinoma may be used as a diagnostic

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tool. Measurements of IgA antibodies to viral capsid antigen (anti-VCA) and of IgG antibodies to early antigen (anti-EA) are the most specific tests, particularly for the undifferentiated types of Nasopharyngeal Carcinoma (NPC).

5 Cancers of the head and neck are staged according to the TNM system of the American Joint Committee on Cancer. The classification of the primary tumor (T) varies depending on its site, size, and extent of invasion of and attachment to the surrounding tissues; only tumors of the oral cavity
10 and oropharynx are classified using the same criteria. When the lesion cannot be measured accurately, the number of sites involved is used to determine the T stage. Cervical lymph nodes (N) are classified by the size, number, and distribution (homolateral or bilateral) of affected nodes.
15 Disease is also classified by the presence or absence of distant metastases (M). The overall stage of the disease is determined from the TNM stage: stage I and stage II diseases, which are considered limited diseases, are accurately assessed by clinical evaluation; stage III, or
20 locally advanced, disease mainly includes larger primary tumors with or without regional nodal spread (T₃N₀, T₁₋₃N₁); and stage IV disease consists of either massive, extensively invasive primary lesions with variable patterns of nodal involvement (T₁₋₄N₂₋₃, T₄N₀₋₁, or locally advanced disease)
25 or any other TN combination with distant metastases (M₁, or metastatic disease).

Although surgery and radiotherapy remain the mainstays of treatment, chemotherapy is playing an increasingly important role in the management of this disease.

30 Chemotherapy is used for palliation of metastatic or recurrent disease or as initial treatment, in combination with surgery and radiotherapy, for locally advanced disease.

Because squamous cell carcinoma of the head and neck is a heterogeneous disease that can arise in multiple sites,
35 the response rates to surgery, irradiation, and chemotherapy vary with the primary site of disease. Thus, prognosis is related not only to stage and histopathologic features but

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also to site and, for patients who are undergoing chemotherapy, to prior treatment.

The strategy for treatment is determined by the stage of disease. For early disease, either surgery or 5 radiotherapy can be employed because they give similar survival results. The choice depends on the expected morbidity from treatment (e.g., loss of speech or functional disfigurement from surgery or severe dryness of the mouth or altered taste from radiotherapy) as well as the urgency of 10 treatment. With more locally advanced disease, surgery and radiotherapy are combined because this approach produces improved control of local disease. Radiotherapy may be administered either preoperatively or postoperatively. 15 Prophylactic radiotherapy is often administered for draining lymph node sites, which are at high risk for microscopic involvement. Chemotherapy has been incorporated into the initial treatment plan for patients with locally advanced disease because five-year disease-free survival is generally low for such patients (10 to 30%) when conventional surgery, 20 radiotherapy, or both are used.

There has been increasing concern that methods of treatment such as surgery, radiotherapy and chemotherapy may adversely affect the patient's natural immunity which probably increases the chances of growth of residual or 25 metastatic tumor cells. This has directed attention not only to early detection and better treatment but also to more research on the possible an etiology of the disease.

Research in the area of allergic reactions of the lung has provided evidence that arachidonic acid derivatives 30 formed by the action of lipoxygenases are related to various disease states. Some of these arachidonic acid metabolites have been classified as members of a family of eicosatetraenoic acids termed leukotrienes. Three of these substances are currently thought to be major components of 35 what has been previously called slow reacting substance of anaphylaxis (SRS-A) and have been designated leukotrienes C₄, D₄, and E₄ (LTC₄, LTD₄, and LTE₄, respectively).

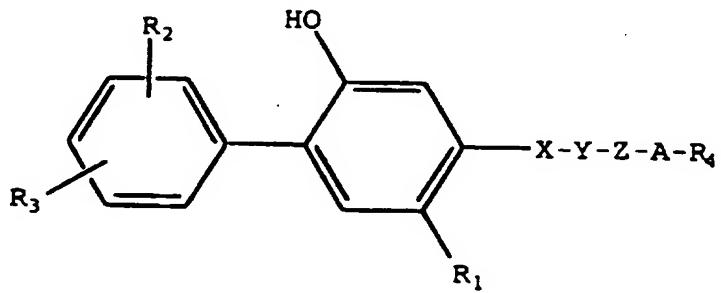
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Another arachidonic acid metabolite, leukotriene B₄ (LTB₄), is a proinflammatory lipid which has been implicated in the pathogenesis of psoriasis, arthritis, chronic lung diseases, acute respiratory distress syndrome, shock, 5 asthma, inflammatory bowel diseases, and other inflammatory states characterized by the infiltration and activation of polymorphonuclear leukocytes and other proinflammatory cells. Thus activated, the polymorphonuclear leukocytes liberate tissue-degrading enzymes and reactive chemicals 10 causing the inflammation. Antagonism of LTB₄ should therefore provide a novel therapeutic approach to treatment of these and other LTB₄ mediated conditions.

Because of the debilitating effects of oral squamous cell carcinoma there continues to exist a need for effective 15 treatments.

Summary of the Invention

This invention provides a method for the treatment or 20 inhibition of oral squamous cell carcinoma which comprises administering to a mammal in need thereof an effective amount of a compound of Formula I



25

I

wherein:

30 R₁ is C₁-C₅ alkyl, C₂-C₅ alkenyl, C₂-C₅ alkynyl, C₁-C₄ alkoxy, (C₁-C₄ alkyl)thio, halo, or R₂-substituted phenyl;

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each R₂ and R₃ are each independently hydrogen, halo, hydroxy, C₁-C₄ alkyl, C₁-C₄ alkoxy, (C₁-C₄ alkyl)-S(O)_q-, trifluoromethyl, or di-(C₁-C₃ alkyl)amino;

5

X is -O-, -S-, -C(=O), or -CH₂-;

Y is -O- or -CH₂-;

10

or when taken together, -X-Y- is -CH=CH- or

—C≡C— ;

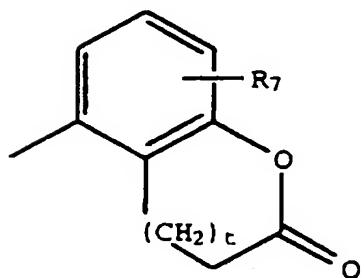
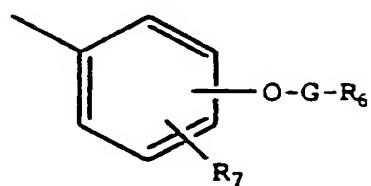
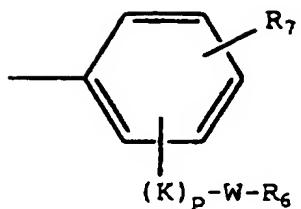
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Z is a straight or branched chain C₁-C₁₀ alkylideny;

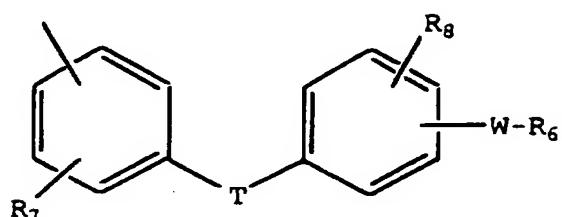
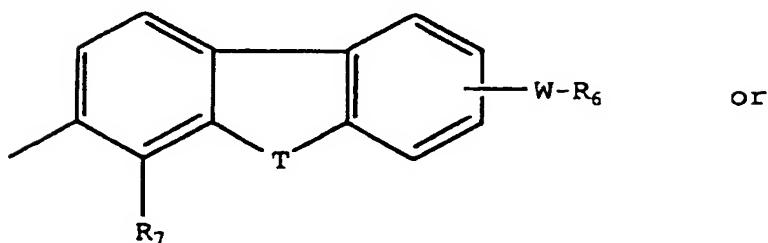
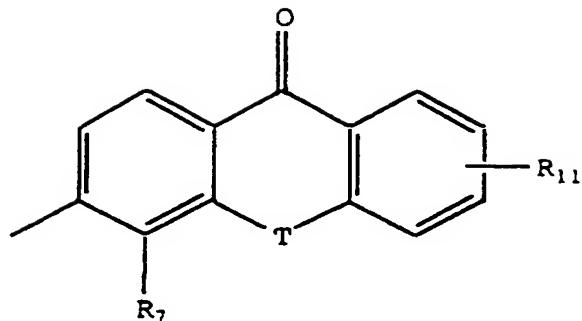
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A is a bond, -O-, -S-, -CH=CH-, or -CR_aR_b-, where R_a and R_b are each independently hydrogen, C₁-C₅ alkyl, or R₇-substituted phenyl, or when taken together with the carbon atom to which they are attached form a C₄-C₈ cycloalkyl ring;

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 R_4 is R_6 

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where,

5 each R6 is independently -COOH, 5-tetrazolyl,
 -CON(R9)2, or -CONHSO2R10;

10 each R7 is hydrogen, C1-C4 alkyl, C2-C5 alkenyl,
 C2-C5 alkynyl, benzyl, methoxy, -W-R6, -T-G-R6,
 (C1-C4 alkyl)-T-(C1-C4 alkylidene)-O-, or
 hydroxy;

R8 is hydrogen or halo;

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each R₉ is independently hydrogen, phenyl, or C₁-C₄ alkyl, or when taken together with the nitrogen atom form a morpholino, piperidino, piperazino, or pyrrolidino group;

5

R₁₀ is C₁-C₄ alkyl or phenyl;

R₁₁ is R₂, -W-R₆, or -T-G-R₆;

10

each W is a bond or straight or branched chain divalent hydrocarbyl radical of one to eight carbon atoms;

15

each G is a straight or branched chain divalent hydrocarbyl radical of one to eight carbon atoms;

each T is a bond, -CH₂-, -O-, -NH-, -NHCO-, -C(=O)-, or -S(O)_q-;

20

K is -C(=O)- or -CH(OH)-;

each q is independently 0, 1, or 2;

p is 0 or 1; and

25

t is 0 or 1;

provided when X is -O- or -S-, Y is not -O-;

30

provided when A is -O- or -S-, R₄ is not R₆;

provided when A is -O- or -S- and Z is a bond, Y is not -O-; and

35

provided W is not a bond when p is 0;

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or a pharmaceutically acceptable salt or solvate thereof.

5

Detailed Description

The following definitions refer to the various terms used throughout this disclosure.

The term "C₁-C₆ alkyl" refers to the straight and 10 branched aliphatic radicals of 1 to 6 carbon atoms such as methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, n-pentyl, 2,2-dimethylpropyl, hexyl, and the like. Included within this definition are the terms "C₁-C₃ alkyl", "C₁-C₄ alkyl" and "C₁-C₅ alkyl".

15 The term "C₂-C₅ alkenyl" refers to straight and branched aliphatic radicals of 2 to 5 carbon atoms containing one double bond, such as -CH=CH₂, -CH₂CH=CH₂, -CH₂CH₂CH=CH₂, -CH₂C(CH₃)=CH₂, -CH₂CH=C(CH₃)₂, and the like.

20 The term "C₂-C₅ alkynyl" refers to straight and branched aliphatic residues of 2 to 5 carbon atoms containing one triple bond, such as -C≡CH, -CH₂-C≡CH, -CH₂CH₂C≡CH, -CH₂CH(CH₃)C≡CH, -CH₂C≡CCH₃, and the like.

The term "C₁-C₄ alkoxy" refers to methoxy, ethoxy, propoxy, isopropoxy, butoxy, sec-butoxy, and tert-butoxy.

25 The term "halo" refers to fluoro, chloro, bromo, and iodo.

The term or "C₁-C₁₀ alkylideny" refers to a 30 divalent radical derived from a C₁-C₁₀ alkane such as -CH₂-, -CH(CH₃)-, -C(CH₃)₂-, -CH(C₂H₅)-, -CH₂CH₂-, -CH₂CH(CH₃)-, -CH(CH₃)CH₂-, -CH(CH₃)CH(CH₃)-, -CH₂C(CH₃)₂-, -CH₂CH(C₂H₅)-, -CH₂CH₂CH₂-, -CH(CH₃)CH₂CH₂-, -CH₂CH(CH₃)CH₂-, -CH₂CH(C₂H₅)CH₂-, -CH₂CH₂CH(C₂H₅)-, -C(CH₃)₂CH₂CH₂-, -CH(CH₃)CH₂CH(CH₃)-, -CH₂CH₂CH₂CH₂-, -CH₂C(CH₃)₂CH₂CH₂-, -CH₂C(CH₃)₂CH₂-, -CH₂CH₂CH(C₂H₅)CH₂-, -CH₂CH₂CH₂CH₂CH₂CH₂-, 35 -CH(CH₃)CH₂CH₂CH₂CH₂-, -CH₂CH₂CH₂CH₂CH₂CH₂-, -(CH₂)₁₀-, and the like. Included within this definition are the terms "C₁-C₄ alkylidene" and "C₂-C₄ alkylidene".

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The term "C₄-C₈ cycloalkyl" refers to a cycloalkyl ring of four to eight carbon atoms, such as cyclobutyl, cyclopentyl, cyclohexyl, 4,4-dimethylcyclohexyl, cycloheptyl, cyclooctyl, and the like.

5 The term "straight or branched chain divalent hydrocarbyl residue of one to eight carbon atoms" refers to a divalent radical derived from a straight or branched alkane, alkene, or alkyne of one to eight carbon atoms. Depending upon the branching and number of carbon atoms, as 10 will be appreciated by organic chemists, such a moiety can contain one, two or three double or triple bonds, or combinations of both. As such, this term can be considered an alkylidene group as defined above containing from 1 to 8 carbon atoms optionally containing one to three double or 15 triple bonds, or combinations of the two, limited as noted in the preceding sentence.

This invention includes the pharmaceutically acceptable base addition salts of the compounds of Formula I. Such salts include those derived from inorganic bases, 20 such as ammonium and alkali and alkaline earth metal hydroxides, carbonates, bicarbonates, and the like, as well as salts derived from basic organic amines, such as aliphatic and aromatic amines, aliphatic diamines, hydroxy alkylamines, and the like. Such bases useful in preparing 25 the salts of this invention thus include ammonium hydroxide, potassium carbonate, sodium bicarbonate, calcium hydroxide, methyl amine, diethyl amine, ethylene diamine, cyclohexylamine, ethanolamine, and the like. The potassium and sodium salt forms are particularly preferred.

30 This invention includes both mono-salt forms, i.e., a 1:1 ratio of a compound of Formula I with a base as previously described, as well as di-salt forms in those instances where a compound of Formula I has two acidic groups. In addition, this invention includes any solvate 35 forms of the compounds of Formula I or salts thereof, such as ethanol solvates, hydrates, and the like.

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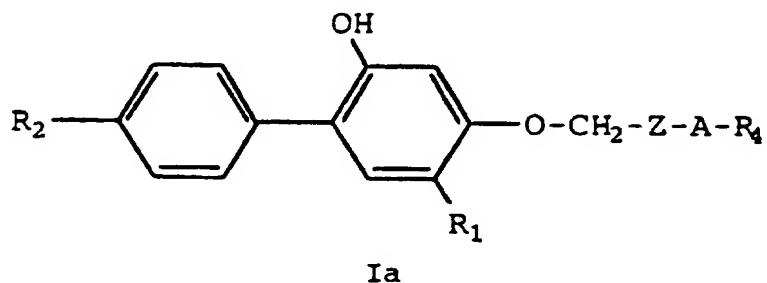
It is recognized that in compounds having branched alkyl, alkylidaryl, or hydrocarbyl functionality, and in those compounds bearing double or triple bonds, various stereoisomeric products may exist. This invention is not limited to any particular stereoisomer but includes all possible individual isomers and mixtures thereof. The term "5-tetrazolyl" refers to both tautomers, ie, (1H)-5-tetrazolyl and (2H)-5-tetrazolyl.

10

Preferred Embodiments

A most preferred group of compounds employed in the methods of the present invention are those compounds of Formula Ia:

15



and pharmaceutically acceptable base addition salts thereof. Especially preferred are those compounds wherein R₂ is halo, particularly fluoro. Preferred R₁ substituents are propyl and especially ethyl.

Preferred Z substituents include C₂-C₄ alkylidene, particularly -CH₂CH₂- and -CH₂CH₂CH₂CH₂- . Preferred A groups include -O-, -CH₂-, -CH(R₇-substituted phenyl)-, and -(CH₃)₂-.

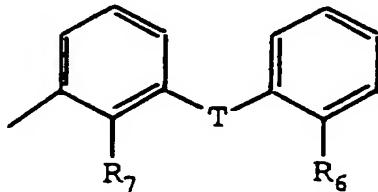
Preferred R₄ groups include -COOH, 5-tetrazolyl, or a mono-, di-, or tri-cyclic group as drawn above wherein there is at least one acidic group attached to a ring, such as -W-COOH, -T-G-COOH, or the corresponding tetrazole derivatives. The preferred W moiety is that of a bond or straight chain C₁-C₄ alkylidene; preferred G moieties are

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straight chain C₁-C₄ alkylidene. It is preferred that R₅ or R₇ be C₁-C₄ alkyl, especially n-propyl.

Particularly preferred groups are those wherein A is -CH(R₇-substituted phenyl)- and R₄ is -COOH or 5-

5 tetrazolyl. Also preferred are those compounds wherein A is -O- and R₄ is



10 Preferred aspects of this substructure are those wherein R₇ is C₁-C₄ alkyl, especially n-propyl, and R₆ is -W-COOH. Particularly preferred are those compounds wherein T is -O- or -S- and W is a bond.

15 Particularly preferred compounds of the instant invention include:

2-[2-propyl-3-[3-[2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]propoxy]phenoxy]benzoic acid;

3-(2-(3-(2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)propoxy)-6-(4-carboxyphenoxy)phenyl)propionic acid;

1-(4-(carboxy-methoxy)phenyl)-1-(1H-tetrazol-5-yl)-6-(2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)hexane;

3-[4-[7-carboxy-9-oxo-3-[3-[2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]propoxy]-9H-xanthene]]propanoic acid; and

5-[3-[2-(1-carboxy)-ethyl]-4-[3-[2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]propoxy]phenyl]-4-pentynoic acid or a pharmaceutically acceptable salt or solvate thereof.

The leukotriene B₄ (LTB₄) antagonists employed in the methods of the present invention may be synthesized

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essentially as described in US Patent No. 5,462,954 issued October 31, 1995, the entire contents of which are herein incorporated by reference.

The following examples further illustrate the preparation of the compounds employed in this invention. The examples are illustrative only and are not intended to limit the scope of the invention. Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. NMR spectra were determined on a GE QE-300 spectrometer.

5 All chemical shifts are reported in parts per million (Δ) relative to tetramethylsilane. Chemical shifts of aromatic protons of quinoline species in DMSO-d₆ are concentration dependent. The following abbreviations are used to denote signal patterns: s = singlet, d = doublet, t = triplet, q =

10 quartet, b = broad, m = multiplet. Infrared spectra were determined on a Nicolet DX10 FT-IR spectrometer. Mass spectral data were determined on a CEC-21-110 spectrometer using electron impact (EI) conditions, a MAT-731 spectrometer using free desorption (FD) conditions, or a VG

15 ZAB-3F spectrometer using fast atom bombardment (FAB) conditions. Silica gel chromatography was performed using ethyl acetate/hexane gradients unless otherwise indicated. Reverse-phase chromatography was performed on MCI CHP20P gel using an acetonitrile/water or methanol/water gradient

20 unless otherwise indicated. Tetrahydrofuran (THF) was distilled from sodium/benzophenone ketyl immediately prior to use. All reactions were conducted under argon atmosphere with stirring unless otherwise noted. Where structures were confirmed by infra-red, proton nuclear magnetic resonance,

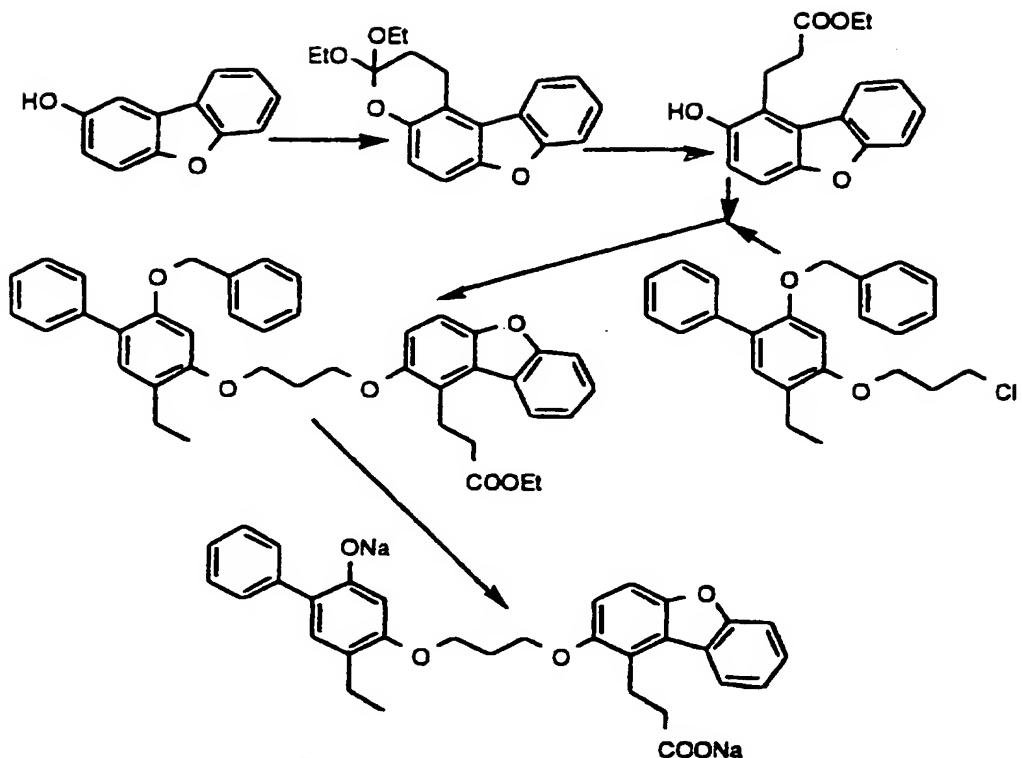
25 or mass spectral analysis, the compound is so designated by "IR", "NMR", or "MS", respectively.

30

Example 1

35 3-[2-[3-[(5-Ethyl-2-hydroxy[1,1'-biphenyl]-4-yl)oxy]propoxy]-1-dibenzofuran]propanoic acid disodium salt

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A. Preparation of 3,3-diethoxy-2,3-dihydro-1H-benzofuro-[3,2-f][1]benzopyran.

5

A solution of 2-hydroxydibenzofuran (5.00 g, 27.2 mmol), triethylorthooacrylate (10.1 g, 54.3 mmol) and pivalic acid (1.39 g, 13.6 mmol) in toluene (100 mL) was refluxed for 18 hours. The mixture was cooled to room temperature and washed once with water and once with a saturated sodium bicarbonate solution, dried over sodium sulfate, filtered and concentrated in vacuo to provide an orange oil. This material was diluted with hexane and maintained at -20°C for 18 hours. The resulting crystals were collected via vacuum filtration to provide 5.67 g (67%) of the desired title intermediate, mp 64°C; NMR (CDCl₃) 7.96 (d, J = 7.8 Hz, 1H), 7.57 (d, J = 8.0 Hz, 1H), 7.46 (t, J = 8 Hz, 1H), 7.35 (m, 2H), 7.06 (d, J = 8.8 Hz, 1H), 3.82 (q, J = 7.2 Hz, 2H), 3.73 (q, J = 6.8 Hz, 2H), 3.35 (t, J = 6.9 Hz, 2H), 2.29 (t, J = 7.0 Hz, 2H), 1.23 (t, J = 7.1 Hz, 6H); MS-FD m/e 312

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(p); IR (CHCl₃, cm⁻¹) 2982, 1494, 1476, 1451, 1434, 1251, 1090, 1054, 975.

Analysis for C₁₉H₂₀O₄:

Calc: C, 73.06; H, 6.45;

5 Found: C, 72.81; H, 6.72.

B. Preparation of 3-[1-(2-hydroxydibenzofuran)]-propanoic acid ethyl ester.

10 A mixture of 3,3-diethoxy-2,3-dihydro-1H-benzofuro-[3,2-f][1]benzopyran (3.50 g, 11.2 mmol) and 10% aqueous hydrochloric acid (5 mL) in ethyl acetate (30 mL) was stirred at room temperature for 1 hour. The resulting mixture was washed once with water, dried over sodium sulfate, filtered and concentrated *in vacuo* to provide a tan solid. Recrystallization from hexane/ethyl acetate provided 3.11 g (98%) of the desired title intermediate as an off-white crystalline material: mp 128-131°C; NMR (CDCl₃) 7.88 (d, J = 7.7 Hz, 1H), 7.59 (d, J = 8.4 Hz, 1H), 7.47 (t, J = 7.2 Hz, 1H), 7.37 (d, J = 8.9 Hz, 1H), 7.36 (t, J = 6.6 Hz, 1H), 7.13 (d, J = 8.8 Hz, 1H), 7.13 (q, J = 8.8 Hz, 2H), 3.43 (t, J = 5.8 Hz, 2H), 3.01 (t, J = 7.7 Hz, 2H), 1.23 (t, J = 7.2 Hz, 3H); MS-FD m/e 284 (100, p), 256 (65), 238 (17); IR (KBr, cm⁻¹) 2985 (b), 1701, 1430, 1226, 1183, 1080.

25 Analysis for C₁₇H₁₆O₄:

Calc: C, 71.82; H, 5.67;

Found: C, 71.90; H, 5.43.

C. Preparation of 3-[2-[3-[[5-ethyl-2-(phenylmethoxy)-[1,1'-biphenyl]-4-yl]oxy]propoxy]-1-dibenzofuran]propanoic acid ethyl ester.

3-[1-(2-Hydroxydibenzofuran)]propanoic acid ethyl ester (625 mg, 2.20 mmol) was dissolved in dimethylformamide (10 mL) and carefully treated at room temperature with 95% sodium hydride (58 mg, 2.4 mmol). When gas evolution had

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ceased, 2-benzyloxy-1-phenyl-5-ethyl-4-(3-chloro-1-propyloxy)benzene (836 mg, 2.20 mmol) was added and the resulting mixture was stirred for 18 hours. The mixture was diluted with ether and washed once with water. The organic 5 layer was dried over sodium sulfate, filtered, and concentrated in vacuo to provide a dark oil. Silica gel chromatography (ethyl acetate/hexane) provided 200 mg (14%) of the desired titled intermediate as a colorless oil: NMR (CDCl₃) 8.11 (d, J = 7.7 Hz, 1H), 7.57 (m, 3H), 7.48 (t, J = 10 7.3 Hz, 1H), 7.20-7.44 (m, 10 H), 7.17 (s, 1H), 7.08 (d, J = 8.9 Hz, 1H), 6.67 (s, 1H), 5.05 (s, 2H), 4.29 (t, J = 6.2 Hz, 2H), 4.26 (t, J = 6.1 Hz, 2H), 4.15 (q, J = 7.2 Hz, 2H), 3.54 (t, J = 8.5 Hz, 2H), 2.67 (m, 4H), 2.37 (t, J = 6.0 Hz, 2H), 1.21 (m, 6H).

15

D. Preparation of 3-[2-[3-[(5-ethyl-2-hydroxy[1,1'-biphenyl]-4-yl)oxy]propoxy]-1-dibenzofuran]propanoic acid disodium salt.

20

To a nitrogen-purged solution of 3-[2-[3-[(5-ethyl-2-(phenylmethoxy)[1,1'-biphenyl]-4-yl)oxy]propoxy]-1-dibenzofuran]propanoic acid ethyl ester (200 mg, 0.318 mmol) in a 1:1 mixture of methanol/tetrahydrofuran (40 mL) was added 10% palladium on carbon (25 mg). The resulting 25 suspension was hydrogenated at 1 atm pressure for 24 hours at room temperature. The mixture was filtered through a short pad of Florisil® and the filtrate concentrated in vacuo. The residue was dissolved in a 1:1 mixture of methanol/tetrahydrofuran (20 mL) and treated with 5N sodium 30 hydroxide solution (2 mL) at room temperature for 24 hours. The resulting mixture was extracted once with diethyl ether. The aqueous layer was acidified with 5N hydrochloric acid solution and extracted twice with methylene chloride. The combined methylene chloride fractions were concentrated in 35 vacuo. The residue was dissolved in a minimum of 1N sodium hydroxide solution and purified on HP-20 resin to provide 53 mg (30%) of the desired title product as a fluffy white

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solid: NMR (DMSO-d₆) 8.12 (d, J = 6.9 Hz, 1H), 7.64 (d, J = 8.2 Hz, 1H), 7.37-7.57 (m, 5H), 7.30 (m, 2H), 7.14 (m, 2H), 6.96 (s, 1H), 6.93 (s, 1H), 4.30 (t, J = 7.3 Hz, 2H), 4.14 (t, J = 5.4 Hz, 2H), 2.48 (m, 4H), 2.23 (m, 4H), 1.10 (t, J = 7.6 Hz, 3H); MS-FAB m/e 555 (88, p + 1), 533 (62); IR (CHCl₃, cm⁻¹) 3384 (b), 2969, 1566, 1428, 1257, 1181.

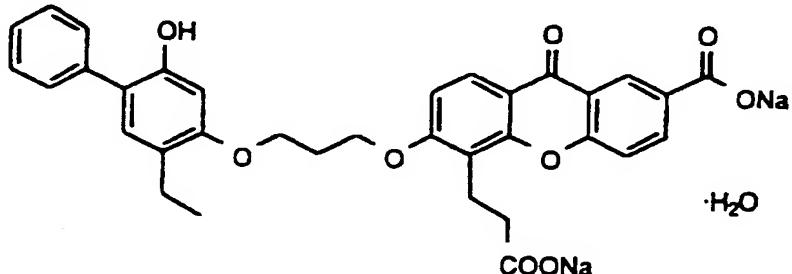
5 Analysis for C₃₂H₂₈O₆Na₂:

Calc: C, 69.31; H, 5.09;
Found: C, 69.51; H, 5.39.

10

Example 2

15 7-Carboxy-9-oxo-3-[3-(2-ethyl-5-hydroxy-4-phenylphenoxy)propoxy]-9H-xanthene-4-propanoic acid disodium salt monohydrate



20 A mixture of 2-benzyloxy-1-phenyl-5-ethyl-4-(3-chloro-1-propoxy)benzene (749 mg, 1.97 mmol), ethyl 7-carboethoxy-3-hydroxy-9-oxo-9H-xanthene-4-propanoate (729 mg, 1.97 mmol), potassium carbonate (1.36 g, 9.85 mmol) and potassium iodide (33 mg, 0.20 mmol) was refluxed for 24 hours. Dimethylsulfoxide (2 mL) was added and heating 25 continued for 24 hours. The reaction mixture was cooled to room temperature, diluted with ethyl acetate, and washed once with water. The organic layer was dried over sodium sulfate, filtered and concentrated in vacuo to reveal a tan solid. This material was dissolved in ethyl acetate (30 mL) 30 and the resulting solution purged with nitrogen. To this solution was added 10% palladium on carbon (120 mg) and the

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resulting suspension hydrogenated at 1 atmosphere of pressure. The solution was filtered and concentrated in vacuo to provide a colorless oil. This material was dissolved in a solution of 1:1 methanol/tetrahydrofuran (30 mL) and treated with 5N sodium hydroxide solution (2 mL) at room temperature for 18 hours. The resulting solution was extracted once with diethyl ether and the aqueous layer acidified with 5N hydrochloric acid solution. The resulting precipitate was collected via suction filtration. This material was converted to the di-sodium salt and purified as described above for the preparation of Example 1(D) to provide 390 mg (56%) of the desired title product as a fluffy white solid: NMR (DMSO-d₆) 12.65 (s, 1H, -OH), 8.65 (s, 1H), 8.28 (dd, J = 8.5, 2.0 Hz, 1H), 8.01 (d, J = 8.9 Hz, 1H), 7.50 (m, 3H), 7.29 (t, J = 7.8 Hz, 2H), 7.17 (m, 2H), 6.93 (s, 1H), 6.89 (s, 1H), 4.26 (m, 4H), 3.12 (m, 2H), 2.47 (m, 2H), 2.23 (m, 2H), 1.10 (t, J = 7.4 Hz, 3H); MS-FAB m/e 627 (24, p), 605 (40), 583 (24), 331 (24), 309 (100); IR (KBr, cm⁻¹) 3419 (b), 2962, 1612, 1558, 1443, 1390, 1277, 1084.

Analysis for C₃₄H₂₈O₉Na₂·H₂O:

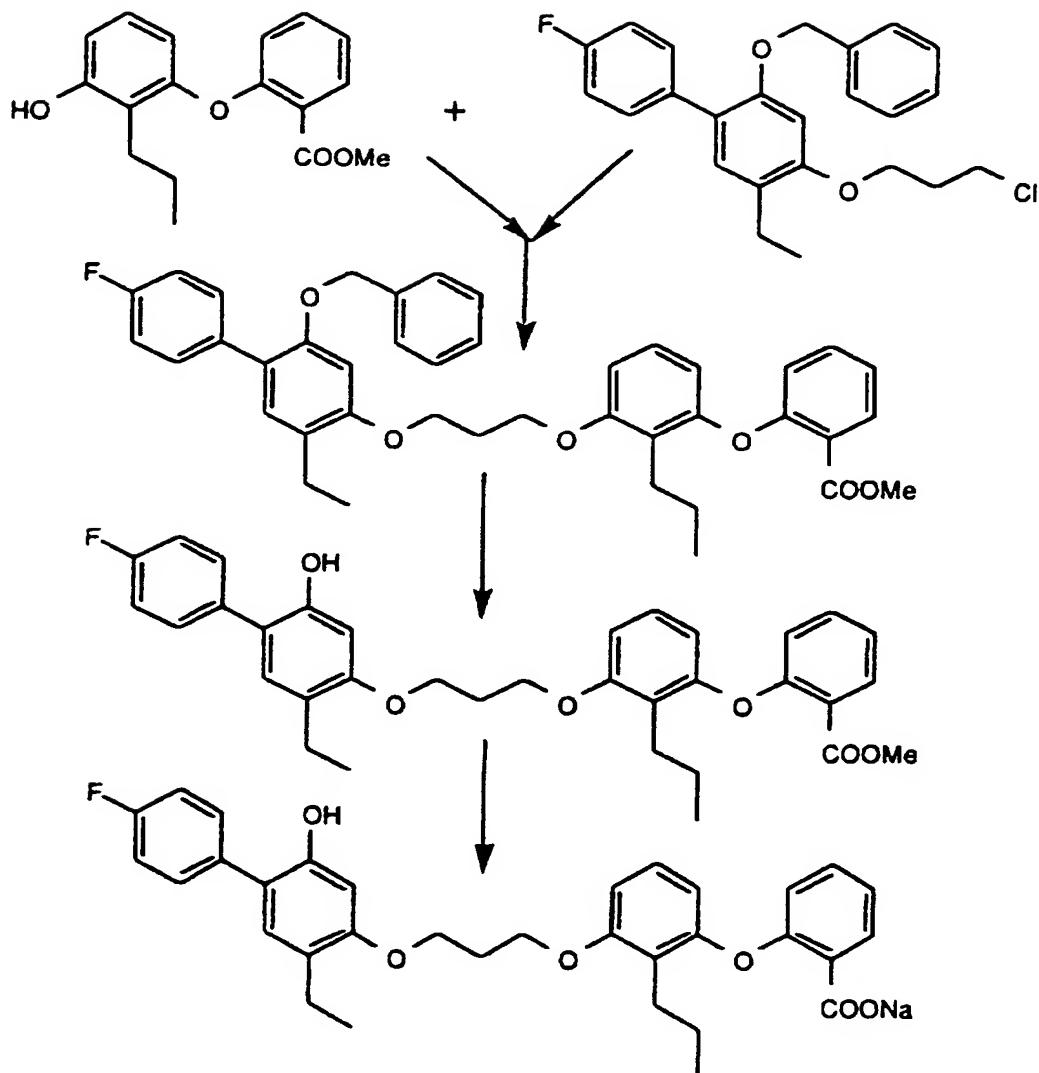
Calc: C, 63.34; H, 4.69;
Found: C, 63.36; H, 4.50.

25

Example 3

2-[2-Propyl-3-[3-[2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]propoxy]phenoxy]benzoic acid sodium salt

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A. Preparation of 2-[2-propyl-3-[3-[2-ethyl-4-(4-fluorophenyl)-5-(phenylmethoxy)phenoxy]propoxy]phenoxy]-5-benzoic acid methyl ester.

A mixture of 2-benzyloxy-1-(4-fluorophenyl)-5-ethyl-4-(3-chloro-1-propyloxy)benzene (20.0 g, 50.2 mmol) and sodium iodide (75.3 g, 502 mmol) in 2-butanone (200 mL) was 10 refluxed for 6 hours. The mixture was diluted with ether and washed once with water. The organic layer was dried over sodium sulfate, filtered, and concentrated in vacuo to provide a colorless oil. This material was dissolved in

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dimethylformamide (100 mL) and treated with 2-(3-hydroxy-2-propylphenoxy)benzoic acid methyl ester (14.4 g, 50.2 mmol) and potassium carbonate (20.8 g, 151 mmol) at room temperature for 24 hours. This mixture was diluted with water and twice extracted with ether. The aqueous layer was separated and back-extracted once with ethyl acetate. The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo* to provide a yellow oil. Silica gel chromatography provided 25.4 g (78%) of the desired title intermediate as a pale golden oil: NMR (CDCl_3) 7.91 (d, $J = 7.8$ Hz, 1H), 7.54 (d, $J = 8.6$ Hz, 1H), 7.52 (d, $J = 8.5$ Hz, 1H), 7.25-7.43 (m, 6H), 7.03-7.38 (m, 5H), 6.84 (d, $J = 8.3$ Hz, 1H), 6.71 (d, $J = 8.1$ Hz, 1H), 6.63 (s, 1H), 6.47 (d, $J = 8.1$ Hz, 1H), 5.03 (s, 2H), 4.24 (t, $J = 5.7$ Hz, 2H), 4.21 (t, $J = 5.8$ Hz, 2H), 3.86 (s, 3H), 2.69 (t, $J = 7.8$ Hz, 2H), 2.64 (t, $J = 7.7$ Hz, 2H), 2.34 (quintet, $J = 6.0$ Hz, 2H), 1.60 (heptet, $J = 5.0$ Hz, 2H), 1.22 (t, $J = 7.5$ Hz, 3H), 0.94 (t, $J = 7.5$ Hz, 3H); MS-FD m/e 648 (p); IR (CHCl_3 , cm^{-1}) 2960, 1740, 1604, 1497, 1461, 1112.

Analysis for $\text{C}_{41}\text{H}_{41}\text{O}_6\text{F}$:

Calc: C, 75.91; H, 6.37;
Found: C, 76.15; H, 6.45.

B. Preparation of 2-[2-propyl-3-[3-[2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]propoxy]phenoxy]benzoic acid methyl ester.

2-[2-Propyl-3-[3-[2-ethyl-4-(4-fluorophenyl)-5-(phenylmethoxy)phenoxy]propoxy]phenoxy]benzoic acid methyl ester (33.0 g, 50.9 mmol) was de-benzylated as described above for the preparation of Example 2 to provide 27.3 g (96%) of the title intermediate as an amber oil: NMR (CDCl_3) 7.90 (dd, $J = 7.8, 1.7$ Hz, 1H), 7.42 (m, 3H), 7.05-7.23 (m, 4H), 6.99 (s, 1H), 6.84 (d, $J = 8.1$ Hz, 1H), 6.70 (d, $J = 8.1$ Hz, 1H), 6.55 (s, 1H), 6.46 (d, $J = 8.1$ Hz, 1H),

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5.05 (s, 1H, -OH), 4.23 (m, 4H), 3.86 (s, 3H), 2.68 (t, J = 7.4 Hz, 2H), 2.62 (q, J = 7.5 Hz, 2H), 2.36 (quintet, J = 6.0 Hz, 2H), 1.60 (hextet, J = 7.7 Hz, 2H), 1.20 (t, J = 7.6 Hz, 3H), 0.94 (t, J = 7.4 Hz, 3H); MS-FD m/e 558 (p); IR 5 (CHCl₃, cm⁻¹) 2965, 1727, 1603, 1496, 1458, 1306, 1112.

Analysis for C₃₄H₃₅O₆F:

Calc: C, 73.10; H, 6.31;
Found: C, 73.17; H, 6.42.

10 C. Preparation of 2-[2-propyl-3-[3-[2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]propoxy]phenoxy]benzoic acid sodium salt.

15 2-[2-Propyl-3-[3-[2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]propoxy]phenoxy]benzoic acid methyl ester (21.5 g, 38.5 mmol) was hydrolyzed as described above for the preparation of Example 2. The acid was converted to the sodium salt and purified as described above for the preparation of Example 1(D) to provide 16.7 g (77%) of the 20 desired title product as a white amorphous solid: NMR (DMSO-d₆) 10.50 (bs, 1H, -OH), 7.51 (m, 3H), 7.20 (t, J = 7.4 Hz, 1H), 7.13 (m, 2H), 7.00 (m, 2H), 6.95 (s, 1H), 6.67 (dd, J = 8.2, 3.3 Hz, 2H), 6.62 (s, 1H), 6.26 (d, J = 8.2 Hz, 1H), 4.14 (t, J = 5.8 Hz, 2H), 4.02 (t, J = 5.7 Hz, 2H), 25 2.60 (t, J = 6.8 Hz, 2H), 2.47 (q, J = 7.3 Hz, 2H), 2.16 (t, J = 5.9 Hz, 2H), 1.45 (hextet, J = 7.5 Hz, 2H), 1.07 (t, J = 7.5 Hz, 3H), 0.81 (t, J = 7.4 Hz, 3H); MS-FAB m/e 568 (38, p + 1), 567 (100, p), 544 (86), 527 (77), 295 (65), 253 (45); IR (KBr, cm⁻¹) 3407 (b), 2962, 1603, 1502, 1446, 1395, 1239, 30 1112.

Analysis for C₃₃H₃₂O₆FNa:

Calc: C, 69.95; H, 5.69; F, 3.35;
Found: C, 69.97; H, 5.99; F, 3.52.

35 The methods of the present invention describe the use of leukotriene antagonists for the treatment or

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prevention of oral squamous cell carcinoma which is characterized by the excessive release of leukotriene B₄.

The term "excessive release" of a leukotriene refers to an amount of the leukotriene sufficient to cause oral squamous cell carcinoma. The amount of leukotriene which is considered to be excessive will depend on a variety of factors, including the amount of leukotriene required to cause the disease, and the species of the mammal involved.

As will be appreciated by those skilled in the art, the success of treating a mammal suffering from or susceptible to oral squamous cell carcinoma characterized by an excessive release of leukotriene with a compound of Formula I will be measured by the regression or prevention of the symptoms of the condition.

15

Assays

Assay 1

The effectiveness of compounds of Formula I to inhibit the binding of tritiated LTB₄ to guinea pig lung membranes was determined as follows.

[³H]-LTB₄ Radioligand Binding Assay in Guinea Pig Lung Membranes

25

[³H]-LTB₄ (196-200 Ci/mmol) was purchased from New England Nuclear (Boston, MA). All other materials were purchased from Sigma (St. Louis, MO). Incubations (555 mL) were performed in polypropylene minitubes for 45 minutes at 30°C and contained 25 mg of guinea pig lung membrane protein (Silbaugh, *et al.*, European Journal of Pharmacology, 223 (1992) 57-64) in a buffer containing 25 mM MOPS, 10 mM MgCl₂, 10 mM CaCl₂, pH 6.5, approximately 140 pM [³H]-LTB₄, and displacing ligand or vehicle (0.1% DMSO in 1 mM sodium carbonate, final concentration) as appropriate. The binding reaction was terminated by the addition of 1 mL ice cold wash buffer (25 mM Tris-HCl, pH 7.5) followed immediately by

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vacuum filtration over Whatman GF/C glass fiber filters using a Brandel (Gaithersburg, MD) 48 place harvester. The filters were washed three times with 1 mL of wash buffer. Retained radioactivity was determined by liquid 5 scintillation counting at 50% counting efficiency using Ready Protein Plus cocktail (Beckman, Fullerton, CA). Nondisplaceable binding was determined in the presence of 1 mM LTB₄ and was usually less than 10% of total binding. Data were analyzed using linear regression analysis of log-logit 10 plots of the values between 10% and 90% of control binding to calculate IC₅₀s and slope factors (pseudo-Hill coefficients). IC₅₀ values thus obtained were corrected for radioligand concentration (Cheng and Prusoff, Biochem. Pharmacol., 22, 3099 (1973)) to calculate K_i values. pK_i is 15 the mean -log K_i for n experiments.

Compounds of the instant invention tested in the above assay were found to have a pK_i of between 7 and 11.

20 The ability of a compound of formula I to effectively treat experimental oral cancer can be evaluated by testing its effect on induction of squamous cell carcinoma in the cheek pouch of Syrian hamsters (Polliack, et al., Br.J.Cancer 23, 781-6, 1969).

25 Assay 2

Tumor development is induced by painting the right cheek pouches of Syrian hamsters (1.5 to 2 months of age) with 0.5% solution of 9,10-dimethyl-1,2-benzanthracene (DMBA) in heavy mineral oil (USP) three times per week for 30 15 weeks. At the completion of the above treatment, the animals are killed, autopsies are performed and both cheek pouches examined for the number and size of tumors. The nature of the lesions are subsequently determined histologically after fixing the tissue in 4% formalin and 35 staining with haematoxylin and eosin. A dose response is obtained by dividing the animals into 4 experimental groups of 10 hamsters each. The groups are: vehicle-treated; 10,

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25, and 50 mg/kg/day of a compound of formula I administered orally to the animals. The effectiveness of a treatment is accessed by comparing the size and number of squamous cell carcinomas and the number of atypical papillomas of the
5 treated group to that of the vehicle control.

Assay 3

Clinical Studies: Human clinical trials may also be employed to assess the value of the compounds of Formula I
10 in treating oral squamous cell carcinoma. The design of clinical trials, use of assessment instruments, and interpretation of these results are well known to clinicians in the field. For example: Five to fifty patients are selected for the clinical study. The patients suffer from
15 squamous cell carcinoma. The study has a placebo control group, i.e., the patients are divided into two groups, one of which receives a compound of formula I as the active agent and the other receives a standard treatment for squamous cell carcinoma. Patients in the test group receive
20 between 30-1500 mg of the drug per day by the oral or parenteral route. They continue this therapy for 3-12 months. Accurate records are kept as to the symptoms and status of the cancer in both groups and at the end of the study these results are compared. The results are compared
25 both between members of each group and also the results for each patient are compared to the status reported for each patient before the study began.

The therapeutic and prophylactic treatments provided by this invention are practiced by administering to a mammal in
30 need thereof a dose of a compound of formula I or a pharmaceutically acceptable salt or solvate thereof, that is effective to inhibit or treat oral squamous cell carcinoma.

The term "inhibit" includes its generally accepted meaning which includes prohibiting, preventing, restraining
35 and slowing, stopping or reversing progression, severity or a resultant symptom. As such, the present method includes

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both medical therapeutic and/or prophylactic administration as appropriate.

While it is possible to administer a compound employed in the methods of this invention directly without any formulation, the compounds are usually administered in the form of pharmaceutical formulation comprising a pharmaceutically acceptable excipient and at least one compound of the present invention. The compounds or formulations of the present invention may be administered by the oral and rectal routes, topically, parenterally, e.g., by injection and by continuous or discontinuous intra-arterial infusion, in the form of, for example, tablets, lozenges, sublingual tablets, sachets, cachets, elixirs, gels, suspensions, aerosols, ointments, for example, containing from 0.01 to 90% by weight of the active compound in a suitable base, soft and hard gelatin capsules, suppositories, injectable solutions and suspensions in physiologically acceptable media, and sterile packaged powders adsorbed onto a support material for making injectable solutions. Such formulations are prepared in a manner well known in the pharmaceutical art and comprise at least one active compound. See, e.g., REMINGTON'S PHARMACEUTICAL SCIENCES, (16th ed. 1980).

In making the formulations employed in the present invention the active ingredient is usually mixed with an excipient, diluted by an excipient or enclosed within such a carrier which can be in the form of a capsule, sachet, paper or other container. When the excipient serves as a diluent, it can be a solid, semi-solid, or liquid material, which acts as a vehicle, carrier or medium for the active ingredient. In preparing a formulation, it may be necessary to mill the active compound to provide the appropriate particle size prior to combining with the other ingredients. If the active compound is substantially insoluble, it ordinarily is milled to a particle size of less than 200 mesh. If the active compound is substantially water soluble, the particle size is normally adjusted by

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milling to provide a substantially uniform distribution in the formulation, e.g. about 40 mesh.

Some examples of suitable carriers, excipients and diluents include lactose, dextrose, sucrose, sorbitol,

5 mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, tragacanth, gelatin, water, syrup, and methyl cellulose.

10 The formulations can additionally include: lubricating agents such as talc, magnesium stearate, and mineral oil; wetting agents; emulsifying and suspending agents; preserving agents such as methyl- and propylhydroxybenzoates; sweetening agents; and flavoring agents. The compositions of the invention can be formulated 15 so as to provide quick, sustained or delayed release of the active ingredient after administration to the patient by employing procedures known in the art.

20 The compounds of this invention may be delivered transdermally using known transdermal delivery systems and excipients. Most preferably, a compound of this invention is admixed with permeation enhancers including, but not limited to, propylene glycol, polyethylene glycol monolaurate, and azacycloalkan-2-ones, and incorporated into a patch or similar delivery system. Additional excipients 25 including gelling agents, emulsifiers, and buffers may be added to the transdermal formulation as desired.

20 For topical administration, a compound of this invention ideally can be admixed with any variety of excipients in order to form a viscous liquid or cream-like 30 preparation.

For oral administration, a compound of this invention ideally can be admixed with carriers and diluents and molded into tablets or enclosed in gelatin capsules.

35 In the case of tablets, a lubricant may be incorporated to prevent sticking and binding of the powdered ingredients in the dies and on the punch of the tabletting machine. For

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such purpose there may be employed for instance aluminum, magnesium or calcium stearates, talc or mineral oil.

Preferred pharmaceutical forms of the present invention include capsules, tablets and injectable solutions.

5 Especially preferred are capsules and tablets.

The therapeutic and prophylactic treatments provided by this invention are practiced by administering to a mammal in need thereof a dose of a compound of formula I or a pharmaceutically acceptable salt or solvate thereof that is 10 effective to inhibit or treat oral squamous cell carcinoma.

Advantageously for this purpose, formulations may be provided in unit dosage form, preferably each dosage unit containing from about 5 to about 500 mg (from about 5 to 50 mg in the case of parenteral or inhalation administration,

15 and from about 25 to 500 mg in the case of oral or rectal administration) of a compound of Formula I. Dosages from about 0.5 to about 300 mg/kg per day, preferably 0.5 to 20 mg/kg, of active ingredient may be administered although it will, of course, readily be understood that the amount of 20 the compound or compounds of Formula I actually to be administered will be determined by a physician, in the light of all the relevant circumstances including the condition to be treated, the choice of compound to be administered and the choice of route of administration and therefore the 25 above preferred dosage range is not intended to limit the scope of the present invention in any way.

The specific dose of a compound administered according to this invention to obtain therapeutic or prophylactic effects will, of course, be determined by the particular 30 circumstances surrounding the case, including, for example, the route of administration the age, weight and response of the individual patient, the condition being treated and the severity of the patient's symptoms.

In general, the compounds of the invention are most 35 desirably administered at a concentration that will generally afford effective results without causing any serious side effects and can be administered either as a

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single unit dose, or if desired, the dosage may be divided into convenient subunits administered at suitable times throughout the day.

While all of the compounds illustrated above exemplify LTB₄ inhibition activity in vitro, we have also discovered that compounds bearing a single acidic group (R₆) are considerably more orally bioactive when administered to mammals compared with those compounds bearing two such acidic groups. Thus, a preferred embodiment when administering compounds of Formula I orally to mammals comprises administering compounds bearing a single acidic R₆ functionality.

The following formulation examples may employ as active compounds any of the compounds of this invention. The examples are illustrative only and are not intended to limit the scope of the invention in any way.

Formulation 1

Hard gelatin capsules are prepared using the following ingredients:

		<u>Quantity (mg/capsule)</u>
25	3-(2-(3-(2-Ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)propoxy)-6-(4-carboxyphenoxy)phenyl)propanoic acid	250
	Starch	200
	Magnesium stearate	10
30		

The above ingredients are mixed and filled into hard gelatin capsules in 460 mg quantities.

Formulation 2

35

A tablet is prepared using the ingredients below:

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		<u>Quantity (mg/tablet)</u>
	1-(4-(Carboxymethoxy)phenyl)-1-(1H-tetrazol-5-yl)-6-(2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)hexane	250
5	Cellulose, microcrystalline	400
	Silicon dioxide, fumed	10
	Magnesium stearate	5

10 The components are blended and compressed to form tablets each weighing 665 mg.

Formulation 3

15 An aerosol solution is prepared containing the following components:

		<u>Weight %</u>
20	3-[4-[7-Carboxy-9-oxo-3-[3-[2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]propoxy]-9H-xanthene]]propanoic acid	0.25
	Ethanol	30.00
25	Propellant 11 (trichlorofluoromethane)	10.25
	Propellant 12 (Dichlorodifluoromethane)	29.75
	Propellant 114 (Dichlorotetrafluoroethane)	29.75

30 The active compound is dissolved in the ethanol and the solution is added to the propellant 11, cooled to -30°C. and transferred to a filling device. The required amount is then fed to a container and further filled with the pre-mixed propellants 12 and 114 by means of the cold-filled method or pressure-filled method. The valve units are then fitted to the container.

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Formulation 4

Tablets each containing 60 mg of active ingredient are

5 made up as follows:

2-[2-Propyl-3-[3-[2-ethyl-5-hydroxy-4-(4-
fluorophenyl)phenoxy]propoxy]phenoxy]-

10	benzoic acid sodium salt	60 mg
	Starch	45 mg
	Microcrystalline cellulose	35 mg
	Polyvinylpyrrolidone (as 10% solution in water)	4 mg
15	Sodium carboxymethyl starch	4.5 mg
	Magnesium stearate	0.5 mg
	Talc	1 mg
	Total	150 mg

20 The active ingredient, starch and cellulose are passed through a No. 45 mesh U.S. sieve and mixed thoroughly. The solution of polyvinylpyrrolidone is mixed with the resultant powders which are then passed through a No. 14 mesh U.S. sieve. The granules so produced are dried at 50-60° and
25 passed through a No. 18 mesh U.S. sieve. The sodium carboxymethyl starch, magnesium stearate and talc, previously passed through a No. 60 mesh U.S. sieve, are then added to the granules which, after mixing, are compressed on a tablet machine to yield tablets each weighing 150 mg.

30

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Formulation 5

Capsules each containing 80 mg of medicament are made as follows:

5	5-[3-[2-(1-Carboxy)ethyl]-4-[3-[2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]propoxy]-phenyl]-4-pentyanoic acid	80 mg
	Starch	59 mg
10	Microcrystalline cellulose	59 mg
	Magnesium stearate	2 mg
	Total	200 mg

The active ingredient, cellulose, starch and magnesium stearate are blended, passed through a No. 45 mesh U.S. sieve, and filled into hard gelatin capsules in 200 mg quantities.

Formulation 6

20 Suppositories each containing 225 mg of active ingredient are made as follows:

25	3-(2-(3-(2-Ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)propoxy)-6-(4-carboxyphenoxy)phenyl)propanoic acid	225 mg
	Unsaturated or saturated fatty acid glycerides to	2,000 mg

30 The active ingredient is passed through a No. 60 mesh U.S. sieve and suspended in the fatty acid glycerides previously melted using the minimum heat necessary. The mixture is then poured into a suppository mold of nominal 2 g capacity and allowed to cool.

35

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Formulation 7

Suspensions each containing 50 mg of medicament per 5 mL dose are made as follows:

5	2-[2-Propyl-3-[3-[2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]propoxy]phenoxy]benzoic acid	50 mg
10	Sodium carboxymethyl cellulose	50 mg
	Sugar	1 g
	Methyl paraben	0.05 mg
	Propyl paraben	0.03 mg
	Flavor	q.v.
	Color	q.v.
15	Purified water to	5 mL

The medicament is passed through a No. 45 mesh U.S. sieve and mixed with the sodium carboxymethylcellulose, sugar, and a portion of the water to form a suspension. The 20 parabens, flavor and color are dissolved and diluted with some of the water and added, with stirring. Sufficient water is then added to produce the required volume.

Formulation 8

25 An intravenous formulation may be prepared as follows:

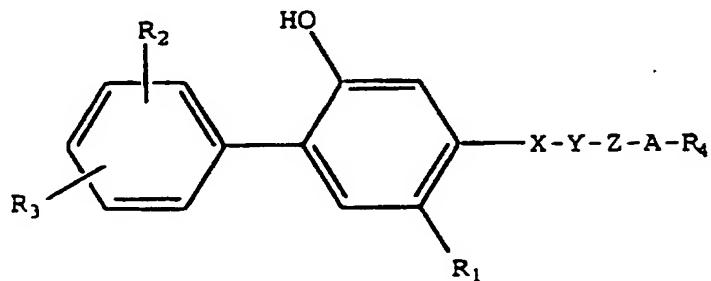
2-[2-propyl-3-[3-[2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]propoxy]phenoxy]benzoic acid	100 mg
Isotonic saline	1,000 ml

30 The solution of the above ingredients generally is administered intravenously to a subject at a rate of 1 ml per minute.

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We claim:

1. A method for treating or inhibiting oral
5 squamous cell carcinoma in a mammal which comprises
administering to a mammal in need thereof an effective
amount of a compound of the formula



10

wherein:

15 R₁ is C₁-C₅ alkyl, C₂-C₅ alkenyl, C₂-C₅ alkynyl,
C₁-C₄ alkoxy, (C₁-C₄ alkyl)thio, halo, or R₂-
substitutedphenyl;

20 each R₂ and R₃ are each independently hydrogen,
halo, hydroxy, C₁-C₄ alkyl, C₁-C₄ alkoxy, (C₁-C₄
alkyl)-S(O)₂-, trifluoromethyl, or di-(C₁-C₃
alkyl)amino;

X is -O-, -S-, -C(=O), or -CH₂-;

25 Y is -O- or -CH₂-;

or when taken together, -X-Y- is -CH=CH- or



30

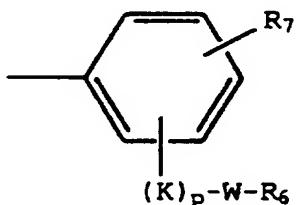
-35-

z is a straight or branched chain C₁-C₁₀ alkylidenyl;

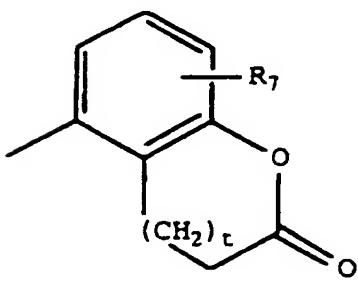
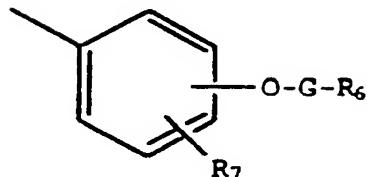
5

A is a bond, -O-, -S-, -CH=CH-, or -CR_aR_b-, where R_a and R_b are each independently hydrogen, C₁-C₅ alkyl, or R₇-substituted phenyl, or when taken together with the carbon atom to which they are attached form a C₄-C₈ cycloalkyl ring;

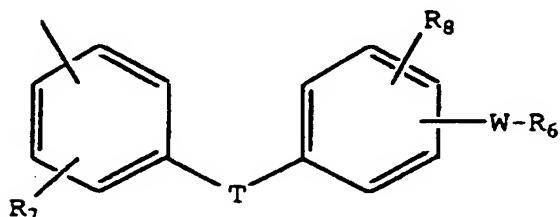
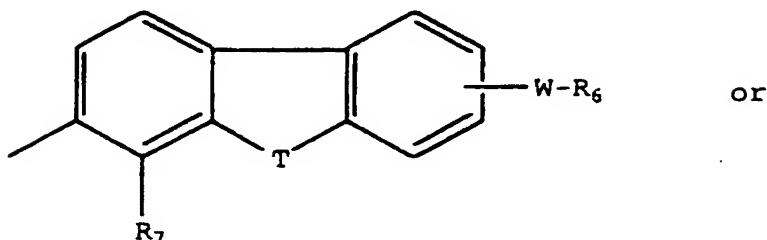
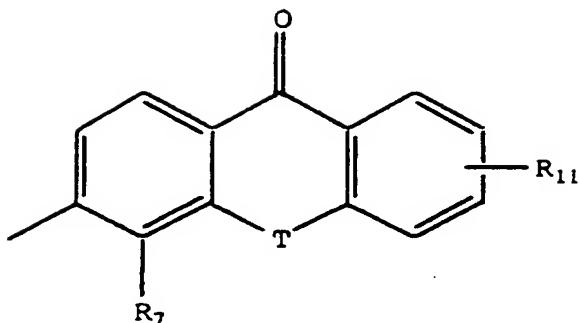
R₄ is R₆



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where,

5 each R6 is independently -COOH, 5-tetrazolyl,
 -CON(R9)2, or -CONHSO2R10;

10 each R7 is hydrogen, C1-C4 alkyl, C2-C5 alkenyl,
 C2-C5 alkynyl, benzyl, methoxy, -W-R6, -T-G-R6,
 (C1-C4 alkyl)-T-(C1-C4 alkylidene)-O-, or
 hydroxy;

R8 is hydrogen or halo;

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each R₉ is independently hydrogen, phenyl, or C₁-C₄ alkyl, or when taken together with the nitrogen atom form a morpholino, piperidino, piperazino, or pyrrolidino group;

5

R₁₀ is C₁-C₄ alkyl or phenyl;

R₁₁ is R₂, -W-R₆, or -T-G-R₆;

10

each W is a bond or straight or branched chain divalent hydrocarbyl radical of one to eight carbon atoms;

15

each G is a straight or branched chain divalent hydrocarbyl radical of one to eight carbon atoms;

each T is a bond, -CH₂-, -O-, -NH-, -NHCO-, -C(=O)-, or -S(O)₂-;

20

K is -C(=O)- or -CH(OH)-;

each q is independently 0, 1, or 2;

p is 0 or 1; and

25

t is 0 or 1;

provided when X is -O- or -S-, Y is not -O-;

30

provided when A is -O- or -S-, R₄ is not R₆;

provided when A is -O- or -S- and Z is a bond, Y is not -O-; and

35

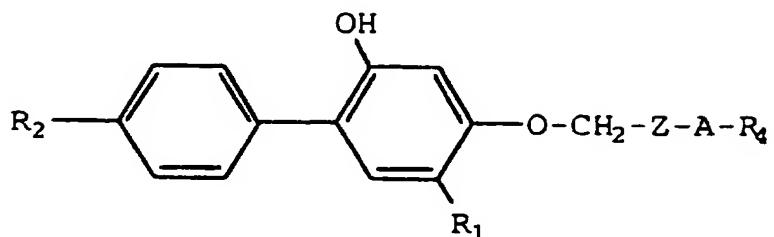
provided W is not a bond when p is 0;

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or a pharmaceutically acceptable salt or solvate thereof.

2. The method as claimed in **Claim 1** employing a compound of the formula

5



or a pharmaceutically acceptable salt or solvate thereof.

10 3. The method as claimed in **Claim 2** employing 2-[2-propyl-3-[3-[2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]propoxy]phenoxy]benzoic acid or a pharmaceutically acceptable salt or solvate thereof.

15 4. The method as claimed in **Claim 2** employing 3-(2-(3-(2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)propoxy)-6-(4-carboxy-phenoxy)phenyl)propionic acid or a pharmaceutically acceptable salt or solvate thereof.

20 5. The method as claimed in **Claim 2** employing 1-(4-(carboxy-methoxy)phenyl)-1-(1H-tetrazol-5-yl)-6-(2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)hexane or a pharmaceutically acceptable salt or solvate thereof.

25 6. The method as claimed in **Claim 2** employing 3-(4-[7-carboxy-9-oxo-3-[3-[2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]-propoxy]-9H-xanthene])propanoic acid or a pharmaceutically acceptable salt or solvate thereof.

30 7. The method as claimed in **Claim 2** employing 5-[3-[2-(1-carboxy)-ethyl]-4-(3-[2-ethyl-4-(4-fluorophenyl)-5-

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hydroxyphenoxy]-propoxy]phenyl]-4-pentynoic acid or a pharmaceutically acceptable salt or solvate thereof.

8. The method as claimed in ~~claims~~ 1 to 7 in
5 which the mammal is a human.

10

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/21953

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : Please See Extra Sheet.
US CL : Please See Extra Sheet.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : Please See Extra Sheet.

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US, A, 5,462,954 A (BAKER ET AL.) 31 October 1995, see entire document.	1-8

Further documents are listed in the continuation of Box C. See patent family annex.

Special categories of cited documents:	
"A" documents defining the general state of the art which is not considered to be of particular relevance	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"B" earlier document published on or after the international filing date	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"C" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another document or other special reasons (as specified)	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"D" document referring to an oral disclosure, use, exhibition or other means	"A" document member of the same patent family
"E" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

21 JANUARY 1998

Date of mailing of the international search report

27 FEB 1998

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/21953

A. CLASSIFICATION OF SUBJECT MATTER:
IPC (6):

A61K 31/495, 31/50, 31/445, 31/44, 31/41, 31/275, 31/19, 31/535

A. CLASSIFICATION OF SUBJECT MATTER:
US CL :

514/239.5, 239.2, 238.8, 237.8, 233.5, 232.8, 252, 318, 332, 340, 343, 346, 347, 351, 381, 520, 521, 570

B. FIELDS SEARCHED

Minimum documentation searched

Classification System: U.S.

514/239.5, 239.2, 238.8, 237.8, 233.5, 232.8, 252, 318, 332, 340, 343, 346, 347, 351, 381, 520, 521, 570

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